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BRIEF REPORT

iGlarLixi Reduces Glycated Hemoglobin to a Greater Extent Than Basal Insulin Regardless of Levels at Screening: Post Hoc Analysis of LixiLan-L

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ABSTRACT

Introduction: The treatment of patients with type 2 diabetes uncontrolled on basal insulin and oral glucose-lowering drugs was investigated previously in the LixiLan-L trial. In the LixiLan-L trial, patients experienced a 6-week run-in with insulin glargine U100 (iGlar) as part of the screening phase, followed by treatment with a fixed-ratio combination of iGlar + lixisenatide (iGlarLixi) or iGlar alone over 30 weeks. In the study reported here, we investigated the achievement of glycemic control in those who completed the 30-week LixiLan-L trial, as assessed by change in glycated hemoglobin (HbA_{1c}) levels from screening, both for the overall category and for screening HbA_{1c} subcategories.

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Methods: This post hoc analysis of the LixiLan-L trial included both the screening phase and the treatment period for 30-week completers and evaluated the change in HbA_{1c} from screening to Week 30, patients reaching $HbA_{1c} < 7\%$ at Week 30, and iGlar and lixisenatide (Lixi) doses at Week 30 overall and according to HbA_{1c} subcategory at screening ($HbA_{1c} \leq 8\%$, $8\% < HbA_{1c} \leq 9\%$, and $HbA_{1c} > 9\%$). Documented symptomatic hypoglycemia during the treatment period was also assessed.

Results: HbA_{1c} reductions (least squares mean) from screening to Week 30 were greater for iGlarLixi than iGlar, both overall (-1.7 vs. -1.1%) and in all subgroups ($HbA_{1c} \leq 8\%$, $8\% < HbA_{1c} \leq 9\%$, and $HbA_{1c} > 9\%$): -1.1, -1.4, -2.4 (iGlarLixi) vs. -0.5, -1.0, -1.8% (iGlar), respectively (all $p < 0.0001$). The end-of-treatment mean HbA_{1c} level for iGlarLixi across all groups was $< 7\%$. More patients achieved an HbA_{1c} of $< 7\%$ with iGlarLixi than with iGlar, both overall (59.9 vs. 31.2%) and within each subgroup [74.2, 54.7, 52.2 (iGlarLixi) vs. 37.2, 31.6, 23.5% (iGlar), respectively]. A higher initial screening HbA_{1c} corresponded with a greater mean reduction in HbA_{1c} for both treatment strategies. In all HbA_{1c} screening categories, the risk of hypoglycemia was not increased with iGlarLixi versus iGlar during the treatment phase.

Conclusion: iGlarLixi controlled HbA_{1c} levels more effectively than iGlar across all HbA_{1c} screening subgroups and in the overall study

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population without increasing the risk of hypoglycemia.

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Keywords: Glycated hemoglobin; iGlarLixi; Insulin glargine U100; Lixisenatide; Type 2 diabetes

INTRODUCTION

Achieving glycemic control is the main objective in the treatment of patients with type 2 diabetes (T2D), with a glycated hemoglobin (HbA_{1c}) target of < 7% recommended for most adults [1, 2]. If HbA_{1c} targets are not reached after initiating basal insulin therapy in patients with T2D, the American Diabetes Association (ADA) guidelines suggest considering a combination injectable therapy, such as rapid-acting insulin prior to the largest meal, glucagon-like peptide-1 receptor agonists (GLP-1 RAs), or a switch to premixed insulin twice daily [2].

iGlarLixi is a once-daily, titratable, fixed-ratio combination of insulin glargine U100 (iGlar) and the GLP-1 RA lixisenatide (Lixi). The complementary actions of iGlar, which predominantly targets fasting plasma glucose (FPG), and Lixi, which predominantly targets postprandial plasma glucose levels, may benefit patients with T2D who are unable to achieve their glycemic targets [3–5]. iGlarLixi was approved in the USA in 2016 for the treatment of adults with T2D inadequately controlled on basal insulin (< 60 U/day) or Lixi, and in Europe in 2017, in combination with metformin, for adults with T2D inadequately controlled with metformin alone or metformin combined with another oral anti-diabetes drug (OAD) or with basal insulin [6, 7]. iGlarLixi has demonstrated superior reduction in HbA_{1c} compared with its individual components of iGlar and Lixi, in the LixiLan-O, LixiLan-L, and LixiLan Proof-of-Concept randomized controlled trials [3–5].

LixiLan-L was a Phase III clinical trial that comprised a 6-week run-in with iGlar and a 30-week randomized treatment period comparing treatment with iGlarLixi ($N = 366$)

versus iGlar ($N = 365$) in patients with T2D previously not sufficiently controlled on basal insulin with or without OADs. The primary analysis showed superior glycemic control as assessed by the change in HbA_{1c} from baseline to Week 30. Furthermore, at Week 30, 54.9% ($n = 201$) of patients treated with iGlarLixi achieved the HbA_{1c} target of < 7.0% compared with 29.6% ($n = 108$) of patients with iGlar alone ($p < 0.0001$) [3]. This post hoc analysis was designed to evaluate the impact of HbA_{1c} levels measured at screening on glycemic control in 30-week completers of the LixiLan-L trial. The inclusion of the screening phase allowed the 6-week run-in with iGlar to be evaluated in conjunction with the 30-week treatment period, providing a more complete investigation of treatment during the LixiLan-L trial.

METHODS

The present study is a post hoc analysis of the LixiLan-L trial (NCT02058160), the methods of which are described briefly below; the complete methodology has been described previously [3].

Trial Design

The LixiLan-L trial was a randomized, open-label, parallel-group, multinational, multicenter Phase III clinical trial for patients previously uncontrolled on basal insulin with or without OADs. The trial was initiated on January 27, 2014 and ended on July 9, 2015 and comprised an 8-week screening phase, which included up to 2 weeks of screening and a 6-week run-in, followed by a 30-week treatment period. The primary efficacy endpoint of the LixiLan-L trial was change in HbA_{1c} from baseline to Week 30.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. Informed consent was obtained from all patients for being included in the study, and the publisher's policy concerning informed consent was followed. The protocol also complied with

the laws, regulations, and any applicable guidelines of the countries in which the study was conducted. Institutional review boards or independent ethics committees at each study site approved the LixiLan-L study protocol.

Data that could identify treatment were masked prior to data review and event adjudication during the LixiLan-L trial. A data monitoring committee reviewed and analyzed the safety data provided by an independent statistical group throughout the LixiLan-L trial.

Study Population

The LixiLan-L trial recruited outpatients with T2D. Eligibility requirements to participate included a diagnosis of T2D for at least 1 year, treatment with a stable basal insulin dose (15–40 U/day) and a FPG level of ≤ 180 mg/dL (10.0 mmol/L) at screening for patients on basal insulin and two OADs, or one OAD other than metformin, or an FPG of ≤ 200 mg/dL (11.1 mmol/L) for patients on basal insulin with or without metformin. The HbA_{1c} level was required to be between 7.5 and 10%, inclusive.

Interventions

At run-in, all patients were on iGlar (100 U/mL), administered once daily; patients previously on other basal insulins were switched to iGlar at the beginning of the run-in. Treatment with OADs other than metformin was stopped. During the run-in, iGlar doses were adjusted according to investigator discretion to achieve a daily fasting self-monitored plasma glucose (SMPG) level of ≤ 140 mg/dL (7.8 mmol/L) while avoiding hypoglycemia.

At the end of the run-in, patients who had an HbA_{1c} of $\geq 7\%$ and $\leq 10\%$, a mean fasting SMPG of ≤ 140 mg/dL (7.8 mmol/L), and an iGlar dose of ≥ 20 and ≤ 50 U/day were randomized (1:1) to receive iGlarLixi or iGlar, stratified by HbA_{1c} at Week -1 ($< 8\%$, $\geq 8\%$) and metformin use at screening (Yes, No). Randomization was performed by an interactive voice response system/interactive web response system according to the randomization scheme provided by the study statistician.

iGlarLixi was provided in two prefilled SoloSTAR® pens (Sanofi, Paris, France). Pen A [2 U iGlar (100 U/mL)/1 µg Lixi ratio] was used to deliver iGlarLixi doses between 10 U (10 U/5 µg) and 40 U (40 U/20 µg); Pen B (3:1 ratio of iGlar:Lixi) was used to deliver iGlarLixi doses between 30 U (30 U/10 µg) and 60 U (60 U/20 µg). iGlar was provided in a prefilled Lantus® SoloSTAR® pen (100 U/mL; Sanofi, Bridgewater, NJ).

In order not to exceed the recommended Lixi starting dose of 10 µg/day, patients randomized to iGlarLixi started on Pen A at a dose of 20 U/day (20 U iGlar/10 µg Lixi) if previously on an iGlar dose of < 30 U/day or on Pen B at a dose of 30 U/day (30 U iGlar/10 µg Lixi) if previously on an iGlar dose of ≥ 30 U/day. iGlarLixi was self-administered prior to breakfast (within 60 min). The iGlarLixi dose was kept stable for 2 weeks. Patients receiving iGlar were started on the same daily dose of iGlar received the day before randomization. iGlar administration time was determined at the beginning of the run-in according to the patient's and/or investigators' preference and was at approximately the same time each day. During treatment, iGlarLixi and iGlar were titrated based on iGlar dose to a fasting SMPG of 80–100 mg/dL (4.4–5.6 mmol/L) while avoiding hypoglycemia.

Lifestyle and diet counseling was provided at the start of the run-in phase and at randomization and was to be continued during the study. Compliance with the diet and lifestyle counseling was to be assessed if sufficient glucose control was not achieved.

The need for rescue therapy was determined according to central laboratory-measured FPG and HbA_{1c} (after Week 12) levels, which were measured if the patient's recorded fasting SMPG values on three consecutive days exceeded the threshold limit for the corresponding period of the study (Electronic Supplementary Table S1).

Post Hoc Analysis

This post hoc analysis of the LixiLan-L trial assessed the efficacy of iGlarLixi compared with

iGlar alone in 30-week completers from the modified intent-to-treat population according to HbA$_{1c}$ level at screening, including both the screening/run-in phase and the 30-week treatment period. Thirty-week completers were defined as patients who completed the 30-week treatment period without rescue therapy. Patients were split into three subcategories according to HbA$_{1c}$ level at screening: HbA$_{1c} \leq$ 8%, 8% < HbA$_{1c} \leq$ 9%, and HbA$_{1c}$ > 9%. The clinical endpoints measuring glycemic control included change in HbA$_{1c}$ from screening to Week 30 and the proportion of patients achieving an HbA$_{1c}$ target of < 7% at Week 30. The dose of iGlar and Lixi at Week 30 and documented symptomatic hypoglycemia during the treatment period, defined as an event with typical symptoms of hypoglycemia that were accompanied by a measured plasma glucose concentration of ≤ 70 mg/dL (≤ 3.9 mmol/L), were also evaluated.

Statistical Analyses

For the overall category, the least squares (LS) mean was estimated from an analysis of covariance (ANCOVA) model with treatment groups, randomization strata of HbA$_{1c}$ (< 8, ≥ 8%) at Week − 1, randomization strata of metformin use at screening (Yes, No), and country as fixed effects, and screening HbA$_{1c}$ value as a covariate. For the screening HbA$_{1c}$ subcategories, the LS mean was estimated from an analysis of variance (ANOVA) model with treatment groups, randomization strata of metformin use at screening (Yes, No), subgroup factor, treatment by subgroup factor, and country as fixed effects. The number (%) of patients with any documented symptomatic hypoglycemia during the 30-week treatment period, as well as the number of events per patient-year, were summarized by treatment and screening HbA$_{1c}$ subcategories.

RESULTS

Patient Characteristics and Demographics

The overall group of 30-week completers comprised 660 patients who completed treatment with iGlarLixi ($n = 327$) or iGlar ($n = 333$) without rescue therapy (Table 1). Patient demographics and characteristics at screening and baseline for the 30-week completers were similar between treatment groups overall and within each HbA$_{1c}$ screening subcategory (Table 1).

HbA$_{1c}$ Reduction

For the 30-week completers of the study, greater reductions in HbA$_{1c}$ from screening to study end was achieved with iGlarLixi than with iGlar ($p < 0.0001$) (Table 2; Fig. 1). The LS mean HbA$_{1c}$ change [± standard error (SE)] was − 1.7% ± 0.1 for iGlarLixi and − 1.1% ± 0.1 for iGlar, with an LS mean difference of − 0.5% ± 0.1 ($p < 0.0001$) for iGlarLixi versus iGlar. Only iGlarLixi-treated patients achieved a mean HbA$_{1c}$ of < 7% at Week 30.

Regardless of the HbA$_{1c}$ screening subcategory, reductions in HbA$_{1c}$ from screening to Week 30 were greater in patients receiving iGlarLixi than in those receiving iGlar ($p < 0.0001$ for all) (Table 2; Fig. 1) and allowed a higher proportion of patients (52.2–74.2 vs. 23.5–37.2%, respectively; Fig. 2) to reach the target HbA$_{1c}$ of < 7% at Week 30. The numerically largest change in HbA$_{1c}$ was observed with iGlarLixi in the HbA$_{1c}$ > 9% screening subcategory (LS mean change − 2.4%). In all HbA$_{1c}$ screening categories, a mean HbA$_{1c}$ of < 7% was only achieved with iGlarLixi.

Treatment Dose

The final insulin dose at Week 30 was generally comparable between treatments, overall and for each HbA$_{1c}$ screening subcategory (Table 2). In the iGlarLixi treatment group, the corresponding final Lixi dose was approximately 17 μg, irrespective of HbA$_{1c}$ level at screening.

Hypoglycemia

In all 30-week completers, the incidence of documented symptomatic hypoglycemia was similar between those receiving iGlarLixi and those

Table 1 Demographics and characteristics at screening or baseline of the 30-week completers of the LixiLan-L trial (30-week completers from the modified intent-to-treat population)

Demographics and clinical characteristics	iGlarLixi				iGlar			
	All completers ($n = 327$)	$HbA_{1c} \leq 8\%$ ($n = 97$)	$8\% < HbA_{1c} \leq 9\%$ ($n = 161$)	$HbA_{1c} > 9\%$ ($n = 69$)	All completers ($n = 333$)	$HbA_{1c} \leq 8\%$ ($n = 94$)	$8\% < HbA_{1c} \leq 9\%$ ($n = 158$)	$HbA_{1c} > 9\%$ ($n = 81$)
Age (years)	59.5 ± 9.4	60.7 ± 9.5	59.1 ± 9.8	58.6 ± 8.2	60.5 ± 8.4	61.4 ± 7.8	59.9 ± 8.1	60.7 ± 9.6
Female (%)	55.4	52.6	57.1	55.1	52.6	51.1	51.9	55.6
Duration of T2D (years)	12.1 ± 6.7	11.9 ± 6.8	11.6 ± 6.1	13.7 ± 7.7	12.1 ± 6.9[a]	12.7 ± 7.1[a]	11.8 ± 6.5	11.9 ± 7.5
Screening BMI (kg/m^2)	31.7 ± 4.2	31.4 ± 4.1	32.0 ± 4.3	31.3 ± 4.2	31.1 ± 4.2	31.0 ± 4.3	31.1 ± 4.3	31.4 ± 4.2
Screening HbA$_{1c}$ (%)	8.47 ± 0.65[a]	7.78 ± 0.18	8.47 ± 0.29[a]	9.45 ± 0.29	8.52 ± 0.66[a]	7.77 ± 0.16	8.49 ± 0.28[a]	9.46 ± 0.28[a]
Baseline HbA$_{1c}$ (%)	8.04 ± 0.67[a]	7.74 ± 0.58	8.05 ± 0.67[a]	8.42 ± 0.60	8.05 ± 0.72[a]	7.62 ± 0.55	8.10 ± 0.67[a]	8.45 ± 0.75[a]
Basal insulin dose at run-in (U/day)	28 ± 8	29 ± 8	28 ± 8	28 ± 8	29 ± 8	28 ± 8	29 ± 8	30 ± 8
iGlar dose at randomization (U/day)	35 ± 9	35 ± 9	35 ± 10	35 ± 9	35 ± 9	34 ± 8	36 ± 9	35 ± 7

All data are presented as the mean ± standard deviation (SD) unless stated otherwise

BMI Body mass index, HbA$_{1c}$ glycated hemoglobin, iGlar insulin glargine U100, iGlarLixi fixed-ratio combination of insulin glargine + lixisenatide, T2D type 2 diabetes

[a] Numbers (n) differed for the duration of T2D in those receiving iGlar (all completers: $n = 332$; HbA$_{1c} \leq 8\%$ subcategory: $n = 93$) and for screening and baseline HbA$_{1c}$ for those receiving iGlarLixi (all completers: $n = 325$; $8\% < HbA_{1c} \leq 9\%$ subcategory: $n = 159$) and iGlar (all completers: $n = 331$; $8\% < HbA_{1c} \leq 9\%$ subcategory: $n = 157$; HbA$_{1c} > 9\%$ subcategory: $n = 80$)

Table 2 Subpopulation analyses at Week 30 for 30-week completers of the LixiLan-L trial (30-week completers from the modified intent-to-treat population)

Parameters	iGlarLixi				iGlar			
	All completers	HbA$_{1c}$ ≤ 8%	8% < HbA$_{1c}$ ≤ 9%	HbA$_{1c}$ > 9%	All completers	HbA$_{1c}$ ≤ 8%	8% < HbA$_{1c}$ ≤ 9%	HbA$_{1c}$ > 9%
HbA$_{1c}$ (n)	325	97	159	69	331	94	157	80
LS mean change ± SE[a]	−1.67 ± 0.07	−1.09 ± 0.10	−1.44 ± 0.09	−2.41 ± 0.12	−1.14 ± 0.07	−0.53 ± 0.10	−1.03 ± 0.09	−1.75 ± 0.11
LS mean difference ± SE[b]	−0.54 ± 0.06	−0.56 ± 0.12	−0.41 ± 0.10	−0.66 ± 0.14				
95% confidence interval	−0.66, −0.42	−0.80, −0.31	−0.59, −0.22	−0.93, −0.39				
p value	< 0.0001	< 0.0001	< 0.0001	< 0.0001				
Dose (n)	327[c]	97	161[c]	69	333	94	158	81
Mean iGlar dose ± SD (U/day)	47 ± 13	48 ± 12	46 ± 13	47 ± 12	47 ± 12	44 ± 12	47 ± 12	49 ± 12
Mean Lixi dose ± SD (µg/day)	17 ± 3	17 ± 3	17 ± 3	17 ± 3				

SE Standard error

[a] Least squares (LS) mean change from screening was estimated using an analysis of covariance (ANCOVA) (all completers) or analysis of variance (ANOVA) (HbA$_{1c}$ subcategories) model, with treatment groups, randomization strata of HbA$_{1c}$ (<8, ≥ 8%) at Week −1 (all completers only), randomization strata of metformin use at screening (Yes, No), subgroup factor (subcategories only), treatment by subgroup factor (subcategories only), and country as fixed effects, and screening HbA$_{1c}$ value as a covariate (all completers only)

[b] iGlarLixi vs. iGlar

[c] For analysis of final Lixi dose, overall $n = 326$; 8% < HbA$_{1c}$ ≤ 9% $n = 160$
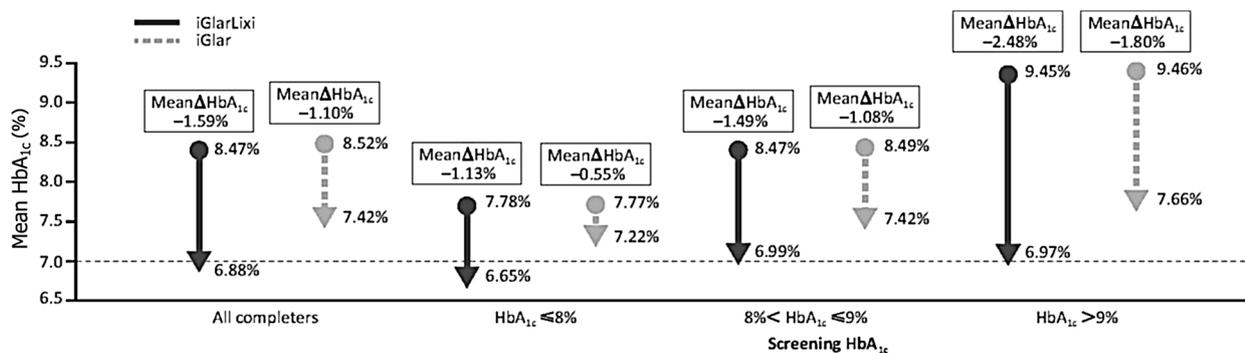
Fig. 1 Mean glycated hemoglobin (HbA_{1c}) change in 30-week completers of the LixiLan-L trial based on screening HbA_{1c} values (30-week completers from the modified intent-to-treat population). All data are observed values. *iGlar* Insulin glargine U100, *iGlarLixi* Fixed-ratio combination of insulin glargine + lixisenatide
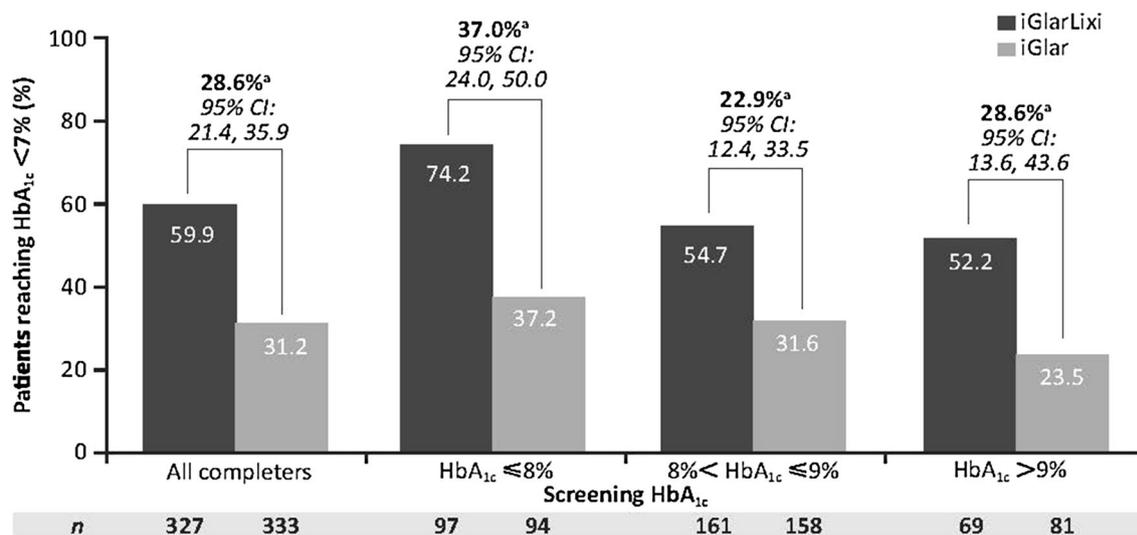
Fig. 2 Patients reaching the $HbA_{1c} < 7\%$ target at Week 30 (30-week completers from the modified intent-to-treat population). [a]Proportion difference = difference in the proportions of patients; weighted average of proportion difference between treatment groups from each strata [randomization strata of metformin use at screening (Yes, No)] using Cochran–Mantel–Haenszel weights. *CI* Confidence interval

receiving iGlar during the 30-week treatment period (Fig. 3). In the subgroup with HbA_{1c} of $\leq 8\%$ at screening, the incidence of documented symptomatic hypoglycemia was numerically lower with iGlarLixi versus iGlar (36.1 vs. 47.9%). For the higher HbA_{1c} screening subcategories the incidences were similar for iGlarLixi and iGlar. Documented symptomatic hypoglycemia events per patient-year were numerically lower with iGlarLixi versus iGlar

overall and in all HbA_{1c} screening subgroups, most prominently in the lowest HbA_{1c} screening category (overall: 2.7 vs. 4.2; $HbA_{1c} \leq 8\%$: 1.8 vs. 5.1; $8\% < HbA_{1c} \leq 9\%$: 2.8 vs. 3.8; $HbA_{1c} > 9\%$: 3.7 vs. 4.2; Fig. 3).

DISCUSSION

In this post hoc analysis of 30-week completers from the LixiLan-L trial, iGlarLixi treatment led
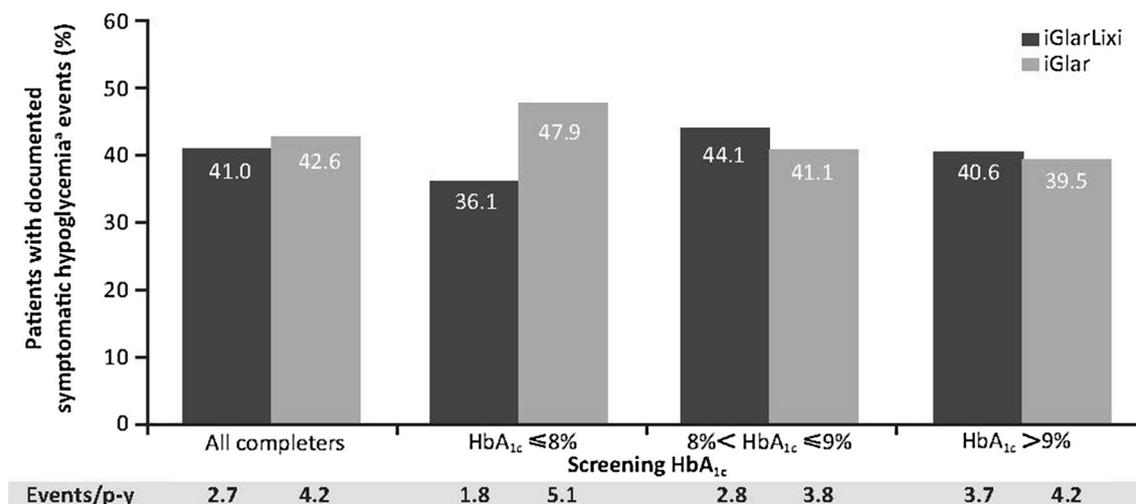
Fig. 3 Documented symptomatic hypoglycemia during the 30-week treatment period (30-week completers; modified intent-to-treat population). [a]Documented symptomatic hypoglycemia includes events with typical symptoms of hypoglycemia and a measured plasma glucose concentration of ≤ 70 mg/dL (≤ 3.9 mmol/L). *p-y* Patient-year

to patients achieving a mean HbA_{1c} level of $< 7\%$ across all HbA_{1c} screening subcategories and overall, meeting the ADA-recommended target. iGlarLixi was more effective than iGlar in controlling HbA_{1c} across all subgroups, including those with a screening HbA_{1c} level of $> 9\%$, without increasing the risk of hypoglycemia. Subgroups with higher initial HbA_{1c} values had the greatest reduction in HbA_{1c} for both treatment strategies.

We investigated the HbA_{1c} reductions achieved from screening to study end for 30-week completers in order to obtain a more complete picture of the treatment provided to the patients during the clinical trial. We also looked at the glycemic control achieved according to the specified screening HbA_{1c} subcategories.

As reported previously for the LixiLan-L trial, mean HbA_{1c} levels decreased from 8.5% at screening to 8.1% at randomization, followed by a LS mean reduction of $- 1.1\%$ to an HbA_{1c} of 6.9% at study end for the iGlarLixi treatment group (modified intent-to-treat/mixed-effect model with repeated measures) [3]. We observed a similar mean HbA_{1c} decrease for 30-week completers according to the present post hoc analysis (HbA_{1c}: 8.5% at screening,

8.0% at baseline, and 6.9% at study end). In a prespecified analysis of the LixiLan-L trial, which analyzed the impact of baseline characteristics, HbA_{1c} reductions from baseline to Week 30 were greater with iGlarLixi than with iGlar for both the baseline $HbA_{1c} < 8\%$ and $HbA_{1c} \geq 8\%$ subcategories ($p < 0.0001$) [8]. Additionally, the higher baseline HbA_{1c} subcategory ($HbA_{1c} \geq 8\%$) demonstrated a greater HbA_{1c} reduction compared with the lower HbA_{1c} subcategory ($< 8\%$) [8], similar to the trend shown here for the screening HbA_{1c} subgroups.

Changes in body weight and lifestyle modifications during the study could also have impacted HbA_{1c} reductions. In the primary analysis of data from the LixiLan-L trial, treatment with iGlarLixi resulted in a mean reduction in body weight from baseline ($- 0.7$ kg), whereas an increase in body weight (0.7 kg) was observed with iGlar at Week 30 ($p < 0.0001$) [3]. In the above-mentioned prespecified analysis of the LixiLan-L trial, the mean weight change was numerically different for patients between baseline body mass index (BMI) subgroups for both treatment arms (iGlarLixi: BMI < 30 kg/m^2: $- 0.1$ kg vs. BMI ≥ 30 kg/m^2: $- 0.9$ kg; iGlar: BMI < 30 kg/m^2: 1.1 kg vs. BMI ≥ 30 kg/

m^2: 0.7 kg); however, the mean ± standard deviation change in HbA_{1c} at Week 30 from baseline was comparable between BMI subgroups for both treatment arms (iGlarLixi: BMI < 30 kg/m^2: −1.1 ± 0.9% vs. BMI ≥ 30 kg/m^2: −1.1 ± 0.9%; iGlar: BMI < 30 kg/m^2: −0.5 ± 0.9% vs. BMI ≥ 30 kg/m^2: − 0.6 ± 0.9%) [8]. In addition, any effect on body weight as a result of the lifestyle and diet counseling provided before screening and during the study would have been applicable to both treatment arms.

Limitations of the LixiLan-L trial included the open-label study design and the relatively short 30-week study duration; longer trials are needed to assess the durability of the glycemic reductions observed [3]. Additionally, the post hoc approach of the present analysis may be considered to be a limitation.

CONCLUSION

In conclusion, irrespective of initial HbA_{1c} screening levels, iGlarLixi can be considered to be an effective new treatment option for controlling HbA_{1c} without an increased risk of hypoglycemia.

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